

Remarks

Claims 1-20 are pending in this application. Claims 2, 4, 6, 8, and 13-17 were withdrawn from consideration by the USPTO for being drawn to non-elected subject matter. Thus, claims 1, 3, 5, 7, 9-12, and 18-20 are currently under consideration.

I. Response to Rejections under 35 U.S.C. § 103

A. Legal Standards for Examination

Before responding directly to the issues raised by the Office Action under Section 103, the legal foundation for sustaining such a rejection will be reviewed. Briefly, an applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. 35 U.S.C. §§ 101, 102, 103, 112. It is the USPTO's duty to issue a patent or establish that the applicant is not entitled to a patent under the law. *In re Warner*, 154 U.S.P.Q. 173, 177 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). Stated a different way, it is not the applicant's responsibility to establish entitlement to a patent. Thus, the initial burden is on the USPTO to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). If no *prima facie* case of obviousness is established, then a rejection under Section 103 cannot properly be sustained. *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). If the USPTO establishes a *prima facie* case of obviousness, then the burden of production shifts to the applicant to provide appropriate

rebuttal, although the burden of persuasion always remains with the USPTO. *Id.* Such rebuttal may include arguments, amendments, and/or presentation of objective indicia of nonobviousness. However, such objective indicia are always relevant to a determination of nonobviousness whether or not a *prima facie* case of obviousness has been established. *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987). To establish a *prima facie* case of obviousness, the USPTO must show all of the limitations of the claimed invention in the prior art. *In re Ehrreich*, 200 U.S.P.Q. 504, 509-11 (C.C.P.A. 1979). The subject matter of the invention must be considered as a whole and through the eyes of a hypothetical person of ordinary skill, not expert skill, in the relevant art at the time the invention was made. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983). References must also be considered as a whole, including subject matter that teaches away from the invention as well as subject matter that suggests the invention, and not for their isolated teachings. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 311 (Fed. Cir. 1983). References may be combined if there would be a "reason to combine" them. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740-41, 1742 (2007). That is, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art" because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and

claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* at 1741. In nonobviousness analysis, one must "guard against slipping into the use of hindsight" and "resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 U.S. at 36, 148 U.S.P.Q. at 474; *KSR*, 127 S. Ct. at 1742. Finally, all the facts in evidence are evaluated, and patentability is determined on the totality of the record. *In re Corkill*, 226 U.S.P.Q. 1005, 1008 (Fed. Cir. 1985). Factual determinations made by the USPTO must be based on a preponderance of the evidence, and legal conclusions must be correct. *In re Caveny*, 226 U.S.P.Q. 1, 3 (Fed. Cir. 1985).

Pursuant to established legal authority, patentability under 35 U.S.C. § 103 requires a four-step factual analysis, which involves (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claimed invention, (3) resolving the level of ordinary skill in the pertinent art, and (4) utilizing the objective evidence of nonobviousness that may have been presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). After all of these factors have been considered, the ultimate legal conclusion on the issue of obviousness must be reached. With the above background in mind the rejections under 35 U.S.C. § 103 will be discussed.

B. Factual and Legal Analysis

Claims 1, 3, 5, 7, 9-11, and 18-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,827,533 ("Needham") in view of U.S. Patent No. 6,353,055 ("Kabanov") and U.S. Patent No. 5,830,430 ("Unger").

Needham discloses membrane-modified liposomes containing active agents aggregated with lipid surfactants. Needham teaches that liposomes consist of at least one lipid bilayer membrane enclosing an aqueous internal compartment. Col. 1, lines 18-19. Liposomes carry drugs either within the aqueous interior space or partitioned into the lipid bilayer. Col. 4, lines 58-62. Partitioning of drugs into the lipid bilayer can damage the drug-retaining ability of the liposome. Col. 4, lines 62-66. Thus, Needham teaches protecting the liposome membrane from deleterious interactions with the drug. Col. 4, line 66, to col. 5, line 2. In contrast, micelles containing drugs are more mobile than liposome preparations, but micelles are more subject to instability, dissolving, and premature drug release upon intravenous administration. Col. 5, lines 3-15. Lipoprotein uptake of micelles also contributes to rapid depletion of drug-containing micelles in the blood stream. Col. 5, lines 16-18. Micelles are not useful for drug administration when delayed or extended administration is desired. Col. 5, lines 19-22. To overcome the problems that liposomes and micelles present for drug delivery, Needham teaches use of drug-containing lipid-surfactant-

micelles encapsulated by liposomes having membranes that contain protective molecules (such as PEG) for inhibiting or preventing fusion of the membrane with the surfactant. Col. 5, line 66, to col. 6, line 30. "Stated another way, liposomes of the present invention contain micellar or emulsified preparations of active agents and contain polymer-grafted lipids in the liposome bilayer in an amount sufficient to inhibit fusion of the membrane with the lipid-active agent aggregates contained therein." Col. 10, lines 59-63.

Kabanov discloses compositions of polynucleotides, polycations, and block copolymers of alkylethers for polynucleotide (i.e., polyanionic, hydrophilic polymers) delivery. Col. 3, lines 3-6. Various architectures of block copolymers are described, col. 3, lines 15-25, and "all of these architectures can be useful for polynucleotide delivery, provided they contain (a) at least one polycationic segment that will bind polynucleotide and (b) at least one water soluble segment that will solubilize the complex formed between the block copolymer and polynucleotide." Col. 3, lines 26-31. Kabanov also discloses compositions further containing cationic, nonionic, or zwitterionic surfactants. Col. 17, line 20, to col. 18, line 45.

Unger discloses cationic lipid compounds for use as carriers in intracellular delivery of bioactive agents. Unger also states that these cationic lipid compounds can be formed into vesicular lipid formulations, such as liposomes and micelles. Unger further

states that bioactive agents can be mixed with the vesicular lipid formulations. Still further, Unger states that vesicular lipid formulations containing the bioactive agent can be administered to an animal. Unger teaches that preferred embodiments of the invention include a gas or gas precursor incorporated into the cationic lipid compositions (column 23, line 22, through column 25, line 39). The gas is disclosed as enhancing delivery of bioactive agents by promoting uptake by cells. Further, at column 25, lines 32-39, Unger teaches that gas precursor-filled or gas-filled vesicles are preferred, because the application of high energy ultrasound, radio frequency, optical energy, and/or heat can be used to rupture the vesicles *in vivo* and thereby promote release of the entrapped gas or precursor and bioactive agent. At column 28, line 53, through column 29, line 16, Unger discloses that, for rupture of vesicles, ultrasound of frequencies from about 0.25 to about 100 megahertz (MHz) are used, with frequencies between about 0.75 and about 3 MHz being preferred and frequencies of about 1 and about 2 MHz being more preferred. Unger further teaches that for very small vesicles, i.e., those where the diameter is less than about 0.5 micron (i.e., 0.5 μm), higher frequencies of sound are generally preferred, because small vesicles are capable of absorbing sonic energy more effectively at higher frequencies of sound.

1. Claims 1, 3, 5, 7, 9-11, and 18-20

The Office Action alleged that it would have been obvious to a person of ordinary skill in the art to combine the teachings of Needham, Kabanov, and Unger to arrive at the presently claimed invention. These references fail to disclose or suggest applying ultrasound at a frequency of 20-100 kHz to a selected site in a patient such that a hydrophobic drug is released from the hydrophobic core of a micelle to the selected site. Unger is the only cited reference that refers to ultrasound, and the range of frequencies disclosed by Unger is 0.25 to 100 MHz (i.e., 250 to 100,000 kHz). Therefore, Unger fails to disclose the range of frequencies claimed. Moreover, Unger fails to suggest using lower frequencies. In fact, Unger states that higher frequencies are needed because small vesicles are capable of absorbing sonic energy more effectively at higher frequencies of sound. That is, Unger suggests using higher frequencies, not lower frequencies. Therefore, neither Unger alone nor the combination of references discloses or suggests using the frequency range claimed.

Unger also teaches the use of gas as a preferred component of his invention. Thus, Unger describes rupture of drug delivery vesicles by application of ultrasonic energy above the cavitation threshold using gaseous bubbles as cavitation nuclei. Applicant's invention uses ultrasound below the cavitation threshold, which does not require the application of gaseous nuclei and makes the presently claimed processes much safer. This is further evidence

that Applicant's presently claimed invention is neither disclosed nor suggested by the cited references.

Still further, Unger discloses cationic surfactants for the making of vesicles for drug delivery. Unger fails to disclose or suggest using nonionic surfactants, such as are used in the presently claimed invention. Although Kabanov discloses using nonionic surfactants for delivery of polynucleotides, Kabanov's complexes for delivery of polyanionic, hydrophilic molecules are not equivalent to the vesicles of Unger. Therefore, applying high-frequency ultrasound to Unger's gas-charged, cationic lipid vesicles would not suggest applying high-frequency ultrasound to Kabanov's complexes, Needham's liposomes, or some hypothetical combination of Needham and Kabanov. Thus, Applicant respectfully asserts that the combination of Needham, Kabanov, and Unger would not suggest to a person skilled in the art to apply low-frequency ultrasound to nonionic micelles for drug delivery.

Further, the cited references teach away from making the presently claimed invention. As discussed above, Unger suggests using higher frequencies of ultrasound, not the lower frequencies claimed. Unger states that for vesicles of diameter less than about 0.5 micron (= 0.5 μm), higher frequencies of sound are generally preferred because small vesicles are capable of absorbing sonic energy more effectively at higher frequencies of sound. These statements are consistent with acoustic theory of oscillating bubbles, which have resonant frequencies (and thus absorb energy

efficiently) that increase linearly as the bubble size decreases. Applicant's disclosure states that the micelles of the presently claimed invention are about 10-35 nm in diameter (= 0.010-0.035 μm or 0.010-0.035 micron; page 2, lines 19-23, and page 5, lines 6-9). According to the teachings of Unger or classical acoustic theory, micelle sizes of 10 to 35 nm would have required optimal frequencies of 30 to 105 MHz. Instead, Applicants did the opposite, the non-standard, the non-obvious, by using lower frequencies. Also, Needham teaches that micelles are subject to instability, being dissolved, premature drug release upon intravenous administration, and lipoprotein uptake, thus leading to rapid depletion of drug-containing micelles in the blood stream. Needham concluded that micelles are not useful for drug administration when delayed or extended administration is desired, such as would be the case in the present invention. Therefore, the combination of Needham, Kabanov, and Unger not only fails to disclose or suggest the presently claimed invention, but teaches away from making the invention.

References must be considered as a whole, including disclosures that teach away from making an invention, as well as disclosures that may suggest making an invention. As briefly reviewed above, Needham relates to drug delivery with liposome-encapsulated micelles, Kabanov relates to delivery of hydrophilic polyanions with complexes containing polycations and block copolymers, and Unger relates to drug delivery with cationic

liposomes and high-frequency ultrasound. It is not clear what the combination of these references, when considered in their entireties, would suggest, but it would not be the present invention. There is no evidence in the record that the cited references were considered in their entireties. In fact the evidence presented, i.e., the incomplete descriptions of the scope and content of the cited references, suggests that the references were not considered in their entireties. The failure to do so is error, and is further evidence that the invention would not have been obvious under Section 103(a).

The failure to consider the references in their entireties leads to a suggestion that the rejection was formulated by picking and choosing certain disclosures, while ignoring others, after having read Applicant's disclosure. This raises the suggestion that hindsight reconstruction was used to improperly formulate the rejection. In cases where the USPTO is accused of using improper hindsight reasoning to reject claims, the USPTO routinely cites *In re McLaughlin*, 170 U.S.P.Q. 209 (CCPA 1971), as standing for the proposition that hindsight reasoning in making a judgment on obviousness is permissible so long as the hindsight reasoning takes into account only knowledge within the level of ordinary skill in the art at the time the invention was made and does not include knowledge gleaned only from the applicant's disclosure. In the first place, *McLaughlin* was a case where the appellant argued that references had been improperly combined to attempt to establish a

prima facie case of obviousness. The court found that there was sufficient motivation in the prior art to make the combination of references. In *dictum* the court made the statement that the USPTO cites. Therefore, *McLaughlin* is *dictum* for the purpose for which the USPTO cites it. In the second place, a few years later the C.C.P.A. stated in *In re Carroll*, 202 U.S.P.Q. 571, 572 (C.C.P.A. 1979) :

One of the more difficult aspects of resolving questions of non-obviousness is the necessity "to guard against slipping into use of hindsight." *Graham v. John Deere Co.*, 383 U.S. 1, 36, 148 U.S.P.Q. 459, 474 (1965). Many inventions may seem obvious to everyone after they have been made. However, 35 U.S.C. 103 instructs us to inquire into whether the claimed invention "would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." Thus, in deciding the issue of obviousness, we must look at the prior art presented from a vantage point in time prior to when the invention was made, and through the eyes of a hypothetical person of ordinary skill in the art.

Moreover, it has been widely recognized that virtually every invention is a combination of elements and that most, if not all, of these will be found somewhere in an examination of the prior art. This reasoning led the Federal Circuit, in *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983) to state:

The test is whether the claimed invention as a whole, in light of all the teachings of the references in their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Still further, the Federal Circuit stated as follows:

Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 4225, 208

U.S.P.Q. 871, 881 (CCPA 1981). . . . It is essential that "the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made . . . to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *Id.* One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

In re Fine, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596, 1599-1600 (Fed. Cir. 1988).

Applicant respectfully submits that if one follows the above guidelines and analyzes the art properly, then the conclusion follows that the claimed invention would not have been obvious to a person of ordinary skill in the art at the time the invention was made.

Another aspect of the claimed invention that is highly relevant to the issue of nonobviousness is consideration of the so-called secondary considerations or objective indicia of nonobviousness. *Graham v. John Deere Co.*, 148 U.S.P.Q. 454 (U.S. 1966). These objective indicia must always be considered along with the factual inquiries of scope and content of the prior art, differences between the prior art and the claimed invention, and the level of skill of one of ordinary skill in the art, and are often the most probative and cogent evidence on the issue. *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987).

An invention that solves a long-felt need in the industry leads to an inference of non-obviousness. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). If the invention would have been obvious to one of ordinary skill in the art, then the solution to the long-felt need would have been supplied much sooner. Further, failure by others skilled in the art to develop the claimed invention or achieve the results of or overcome the problems solved by the claimed invention provides direct evidence that the claimed invention would have been non-obvious to those skilled in the art at the time of the invention. *Standard Corp. v. Tennessee Valley Authority*, 1 U.S.P.Q.2d 1337, 1344-45 (Fed. Cir. 1986). Both of these objective indicia, long-felt need and failure of others, exist in the present case.

The idea of a "magic bullet" that would leave healthy tissue alone and hit just its selected target was first formulated by Paul Ehrlich more than a century ago. Ever since, many research groups across the world have worked and continue to work toward this ultimate goal. Successful drug targeting and controlled release remain an unfulfilled dream and a hot topic of many scientific conferences. If the presently claimed approach to solving the drug targeting and controlled release problem were obvious, then the problem would have been solved decades ago. Applicant is the first to show *in vivo* that ultrasound used in combination with polymeric micelles results in significantly enhanced drug accumulation in tumor cells that significantly exceeds drug accumulation in other

organs. A presentation given at the AAPS meeting in October 2003 presented data showing *in vivo* drug targeting to ovarian carcinoma tumors using ultrasound-activated drug delivery in polymeric micelles.

Thus, the long-felt need in the industry and the failure of others to target drugs to selected locations both support the inference that the presently claimed invention is unobvious.

Further, acclaim by experts or professional approval can also lead to an inference of significant technical accomplishment, and hence nonobviousness. *Burlington Industries, Inv. v. Quigg*, 3 U.S.P.Q.2d 1436 (Fed. Cir. 1987). In this connection, Dr. Rapoport has been an invited speaker at highly acclaimed international meetings. One of her presentations was awarded the First Prize. A short list of her presentations on the subject of the invention at national and international meetings during a recent three year period include: American Chemical Society, Orlando, Florida, spring 2001; Particles, Orlando, Florida, 2001; National Institutes of Health, Bethesda, Maryland, 2002; Controlled Release Society, Paris, France, 2001; Controlled Release Society, Glasgow, Scotland, 2003; ISMAR, Rhodos, Greece, 2001; EMBEC, Vienna, Austria, 2002; Ultrasonics, Granada, Spain, 2003; IACIS, Iguazu Falls, Brazil, 2003; and AAPH, Salt Lake City, Utah, 2003.

Following Dr. Rapoport's presentation at the American Chemical Society meeting in 2001, several articles were written about her work in articles published in paper form (Drug Discovery Today) and

on the World Wide Web. For instance, Reuters Health described her work on the Web in Today's Health News, which is reproduced as follows:

Today's Health News

Researchers developing stealth anti-cancer drugs

SAN DIEGO, Apr 05 (Reuters Health) - Researchers in Utah are working on a new drug delivery system to treat cancer tumors.

"We had this idea of creating a 'magic bullet'--we wanted to make an anti-cancer drug that could bypass normal healthy tissue and target tumor cells," lead researcher Dr. Natalya Rapoport of the University of Utah, Salt Lake City, told Reuters Health. "Another one of our goals is to create a treatment that will overcome the problems that cancer patients face with drug resistance," she added.

To do this, Rapoport and her colleagues encapsulated an anti-cancer drug in polymer micelles--very tiny spheres that have a hollow core surrounded by a shell. The shell helps keep the contents of the core from being recognized by the body's immune system, Rapoport explained.

The preliminary research findings were presented here Thursday at the national meeting of the American Chemical Society.

The drug delivery system is very stable and can travel in the bloodstream without breaking down very quickly. Since tumors have voracious appetites in order to maintain their accelerated growth, they require a substantial amount of nutrients. This means that they are constantly growing new blood vessels to bring in more blood to fuel their growth. The blood vessels of tumors are different from normal blood vessels in the body and are much more permeable, allowing the little capsules to gain entry into the tumor cell, Rapoport noted.

"We have found that the anti-cancer drugs are able to collect in the cancer tumor cells," she said. "This fact may also help limit the amount of exposure of healthy tissue to the anti-cancer drug, which may reduce side effects to the drugs," she pointed out.

Once the drug is inside the tumor, the scientists plan to use ultrasound (high-frequency sound waves) to help the anti-cancer drug break free from the container and kill the tumor cells.

In cell cultures, the researchers have used the technique to successfully deliver the anti-cancer drug into cancer cells that are naturally resistant to existing chemotherapy drugs.

So far, the team has only begun testing the technique in rats, but if these tests go according to plan, the researchers are looking forward to human trials in about 3 years, Rapoport stated.

This evidence points to the recognition of experts in the field to significant technical accomplishment, and hence nonobviousness.

Finally, *Graham* requires that certain factual findings be established as a prerequisite to making a legal determination under Section 103. Among these factual findings is a determination of the level of skill of a person of ordinary skill in the art. Indeed, without making such a determination it defies logic to conclude that a claimed invention would have been obvious to the person of ordinary skill in the art. There is no evidence in the record that the level of skill of the person of ordinary skill in the art was even considered, much less determined. Therefore, it was premature and improper for the Office Action to allege that the claimed invention would have been obvious under Section 103.

For the reasons set out above, namely, that (1) the combination of cited references fails to disclose or suggest each and every limitation of the invention as claimed, (2) the cited

references teach away from making the claimed invention, (3) the cited references were not considered in their entireties, (4) the Office Action resorted to picking and choosing some disclosures, ignoring others, after having read Applicant's disclosure, thus using hindsight reconstruction to reject the claims, (5) objective indicia of nonobviousness point to the nonobviousness of the claimed invention, and (6) the USPTO failed to fulfill the mandates of *Graham* by failing to establish the level of skill of a person of ordinary skill in the art, a *prima facie* case of obviousness was not established by the USPTO. When all the evidence on the record is considered, the preponderance of the evidence as to the factual underpinnings of a legal conclusion under Section 103 clearly weighs in favor of a conclusion that the invention as claimed would not have been obvious to a person of ordinary skill in the relevant art at the time the invention was made. Accordingly, withdrawal of the rejection under Section 103 is respectfully requested.

2. Claim 12

Claim 12 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Needham in view of Kabanov and Unger in further view of U.S. Patent No. 4,322,934 ("Emanuel").

The scope and content of Needham, Kabanov, and Unger were summarized above, and that summary is incorporated herein by reference. Emanuel discloses ruboxyl and a method of producing it.

Claim 12 is dependent on claim 1 and certain intervening dependent claims. Therefore, claim 12 incorporates by reference all of the limitations of claim 1 and those intervening dependent claims. The combination of Needham, Kabanov, Unger, and Emanuel fails to render claim 12 obvious for the same reasons that Needham, Kabanov, and Unger fail to render claim 1 obvious, as stated above. That is, the addition of Emanuel to the combination of references does not cure the deficiencies of Needham, Kabanov, and Unger: (1) the combination of cited references fails to disclose or suggest each and every limitation of the invention as claimed, (2) the cited references teach away from making the claimed invention, (3) the cited references were not considered in their entireties, (4) the Office Action resorted to picking and choosing some disclosures, ignoring others, after having read Applicant's disclosure, thus using hindsight reconstruction to reject the claims, (5) objective indicia of nonobviousness point to the nonobviousness of the claimed invention, and (6) the USPTO failed to establish the level of skill of a person of ordinary skill in the art, one of the required factual findings that must be made prior to reaching a legal conclusion on the issue of nonobviousness. Thus, a *prima facie* case of obviousness was not established by the USPTO. When all the evidence on the record is considered, the preponderance of the evidence as to the factual underpinnings of a legal conclusion under Section 103 clearly weighs in favor of a holding that the invention as claimed would

not have been obvious to a person of ordinary skill in the relevant art at the time the invention was made. Accordingly, withdrawal of the rejection under Section 103 is respectfully requested.

II. Response to Double Patenting Rejection

Claims 1 and 3 were rejected on the ground of obviousness-type double patenting over claim 22 of U.S. Patent No. 6,649,702 ("Rapoport"). The Office Action stated that the difference between claims 1 and 3 and Rapoport is that Rapoport does not expressly disclose an ultrasound frequency of 20-100 kHz for releasing the drug from the carrier. The Office Action concluded that this deficiency is cured by the teachings of Unger.

The scope and content of Unger was summarized above, and that summary is incorporated herein by reference. Briefly, Unger discloses that, for rupture of vesicles, ultrasound of frequencies from about 0.25 to about 100 MHz (250 to 100,000 kHz) are used. Unger further teaches that for vesicles the size of those used in Rapoport high frequencies of sound should be used. Unger further teaches application of ultrasonic energy above the cavitation threshold, whereas Applicant's invention uses ultrasound below the cavitation threshold. Therefore, the combination of Rapoport and Unger fails to disclose or suggest each and every limitation of the invention as claimed, and the combination further teaches away from making the claimed invention. Therefore, claims 1 and 3 are not obvious over claim 22 of Rapoport. Thus, the obviousness-type

double patenting rejection should be withdrawn, and such withdrawal is respectfully requested.

III. Conclusion

Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicant respectfully requests reconsideration and allowance of Claims 1, 3, 5, 7, 9-12, and 18-20 and passage of this application to issue.

DATED this 23rd day of May, 2008.

Respectfully submitted,



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